REPLACED BY ART 34 AMDT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
80277 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/09496	27.08.2003	27.08.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K7/48		
Applicant		
SOCIETE DES PRODUITS NESTLE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.03.2004	19.01.2005
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/09496

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-40 as originally filed

Claims, Numbers

1-37 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/09496

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-12, 14-37

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-12, 14-37 (all of them in part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	24-32, 35, 36
	No:	Claims	1-4, 10-23, 33, 34, 37
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-37
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	18-34 and 36-37

2. Citations and explanations

see separate sheet

Item I

The amendments filed with the letter dated 13.05.2004 introduce subject-matter which extends beyond the concept of the application as filed, contrary to Art. 34(2)(b) PCT. The amendments concern the expression "a polypeptide or peptide, which is **not** an antibody" of claim 1. No basis for such amendment can be seen in the description. For instance, page 10, first paragraph refers only to "polypeptide or a peptide, in particular hydrophobic peptides, more preferably an antibody".

Item III

Independent claims 18-34, 36, 37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(I) PCT).

For the assessment of the present claims 18-34 and 36-37 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The present wording of claims 18-34 and 36-37 is not allowable for the following reasons:

Claims 18-23: "the prevention and/or treatment of damages in epithelial tissue produced by a stress situation" includes inter alia, the medical treatment of cancer.

Claims 24-32: the scope of these claims may imply an "in vivo" treatment.

Claim 33-34. The subject-matter of these claims relates to a treatment of cancer.

Claim 36. The subject-matter of claim 36 refers to a method of testing. The utilisation of

test animal for test purposes in industry is patentable if does not include human beings. In this case, "animals" is a broad concept which also includes human beings.

Claim 37 relates to gene therapy.

The examination of claims 18-34 and 36-37, as far as it can be done (see last paragraph of item III) has been based on the alleged effects.

Independent of that, the International Search Report has not been established for claims 1-12 and 14-37 (all of them in part as far as they do not relate to the compounds of claim 13).

Consequently, the examination has only been carried out for those parts of the claims which appear to be supported and disclosed (Art. 34(4)(a)(ii) PCT) and which have been searched Rule 66.1(e)PCT, namely those parts relating to the compounds mentioned in claim 13.

Item V

Reference is made to the following documents:

D1: WO 02/076401 A (GILLESSEN SILKE ;DANA FARBER CANCER INST INC (US); DRANOFF GLENN () 3 October 2002 (2002-10-03)

D2: WO 00/62787 A (UNIV CALIFORNIA) 26 October 2000 (2000-10-26)

D3: WO 99/22728 A (ARCH DEV CORP ;LIAO SHUTSUNG (US); HIIPAKKA RICHARD A (US)) 14 May 1999 (1999-05-14)

D4: WO 01/79152 A (YISSUM RES DEV CO ;DAGAN ARIEH (IL); GATT SHIMON (IL)) 25 October 2001 (2001-10-25)

D5: WO 01/12208 A (DRIEU KATY ;SOD CONSEILS RECH APPLIC (FR); UNIV GEORGETOWN (US); P) 22 February 2001 (2001-02-22)

D6: K. SHARMA: "Death the Fas way: regulation and pathophysiology of CD95 and its ligand" PHARMACOLOGY AND THERAPEUTICS, vol. 88, 2000, pages 333-347, XP002238439

In view of the above (see item III) it is not possible at present to give a complete opinion on novelty and inventive step. However, the following should be taken into account.

Novelty (Art. 33(2) PCT)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4, 10-23, 33,34 and 37 is not new in the sense of Article 33(2) PCT.

The document D2 discloses an oligonucleotide which modifies CD1d expression and which can be used in cancer immunotherapy (page 2, paragraphs 2 and 4). Accordingly, the subject-matter of claims 1-4, 14-17 and 18-21 is not new.

Documents D3-D6 disclose compounds in the treatment of various disorders mentioned in the present application. The fact that the claimed substance is "capable to block of modify endogenous CD1d function" and that is "obtainable" by a specific process of claim 1 do not confer novelty to the product per se. Documents D3-D6 describe compounds fall within the scope of claim 13 for the treatment of the damages in epithelial tissues by a stress situation and/or the treatment of hair loss. To be more specific:

D3 disclose epigallocatechin gallate, a component of green tea for the treatment of cancer, skin disorders and baldness (claims 2-5 and table I).

D4 disclose sphingosylphosphorylcholine for the treatment of cancer diseases and for killing drug-resistant cancer cells (page 9, paragraphs 4,5).

D5 describe the use of ginkgo extract or isolated Ginkgolide B in the treatment of cancer (claim 1).

D6 disclose CD95/APO-1/Fas.

Therefore documents D3-D6 take away the novelty of claims 1-4, 10-23, 33, 34 and 37.

Inventive Step (Art. 33(3) PCT)

As far as new, the subject-matter of independent claims 24, 35 and 36 does not seem to be inventive. The screening assays of claim 24 seem to be common practice in the art and do not appear to lead to any surprising effect (see D2, example IV, V). For the same reasons the use of cells expressing CD1d in such an assays (claim 35) or the use of CD1d animal as test models is not considered to be inventive.

Accordingly, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 24-32 and 35-36 is not inventive in the sense of Article 33(2) PCT.

Claims

1. A substance capable to block or modify endogenous CD_{1d} function, selected from the group consisting of

a polynucleotide antisense to a sequence comprised by the CD_{1d}-gene and/or the CD_{1d}-mRNA;

a polynucleotide antisense to a sequence comprised by the glucosylceramide synthase gene and/or the glucosylceramide synthase mRNA;

a polynucleotide sense to a sequence comprised by the sphingomyelinase or ceramide synthase gene and/or the sphingomyelinase or ceramide synthase mRNA;

a polypeptide or peptide, which is not an antibody, binding to CD_{1d} and essentially blocking or modifying CD_{1d} function; and

a lipid, which is a sterol, fatty acid, glyceride or phosphatidylinositol phosphate.

2. The substance according to claim 1, which is a compound reducing the transcription and/or translation of the CD_{1d} gene.

3. The substance according to claim 1 and 2 which is derived from plants, microbes or animals or ingredients of green tea or carotenoid.

4. The substance according to claim 1, which is a ligand of a receptor belonging to the TNF super-family, in particular CD95/APO-1/Fas.

5. The substance according to any of the preceding claims for the preparation of a carrier for the prevention and/or treatment of the detrimental effects of stress to epithelial cells and/or hair loss.

6. A composition, containing at least a substance according to any of the preceding

claims.

7. A composition according to claim 6, which is a food composition, a cosmetic composition or a pharmaceutical composition.

8. The composition according to claim 7, which is milk, yogurt, curd, cheese, fermented milks, milk based fermented products, ice-creams, milk based powders, infant formulae, cereal products, fermented cereal based products, mineral water, chocolate or pet food, or lotions, shampoos, creams, sun-screens, after-sun creams, anti-ageing creams and/or ointments or tablets, liquid, dried oral supplement, wet oral supplement, dry tube-feeding or wet tube-feeding or an anti-cancer drug.

9. Use of a substance according to the claims 1 to 5 or a composition according to any of the claims 6 to 8 for the prevention and/or treatment of damages in epithelial tissues produced by a stress situation and/or for the prevention and/or treatment of hair loss.

10. The use of a substance or of a composition according to claim 9 for preventing and/or treatment of damages in epithelial tissues by a stress situation, wherein the lipid is a phytochemical, especially a natural or synthetic polyphenol, a ginkgolide or vitamin.

11. The use according to claim 9, wherein the stress, situation is a chemical stress, a biological stress or a physical stress.

12. The use according to any of the claims 11, wherein the chemical stress is exerted by exposure to oxidants or carcinogens, or wherein the biological stress is exerted by exposure to bacteria, viruses, fungi, lipids derived from surrounding cells and/or microbes, or wherein the physical stress is exerted by exposure to UV-irradiation.

13. The use according to any of the claims 9 to 12, wherein the damage is skin burning and/or blistering, cataract formation, epidermal hyperplasia, cancer, inflammation, immune suppression, skin ageing.

14. The use according to any of the claims 9 to 13, wherein the epithelial cells are derived from the skin, gut, eye, lung, prostate, liver, breast, kidney and/or the uterus.

15. The use according to claim 14, wherein the cancer is breast cancer, colon cancer, prostate cancer, liver cancer, pancreatic cancer, kidney cancer, non-melanoma and melanoma skin cancers.

16. A method for identifying CD_{1d} blocking or modifying substances, which comprises the following steps:
    (a) exposing epithelial cells to a substance of interest,
    (b) subjecting the epithelial cells to a stress situation,
    (c) determining the effect of said stress to said epithelial cells by screening for one or more of the following assays,
        (i) epithelial hyperplasia (H&E),
        (ii) epithelial proliferation (BrUd, PCNA),
        (iii) epithelial apoptosis (TUNEL),
        (iv) p53 mutation accumulation,
        (v) quantitative and qualitative assessment of epithelial lipids,
        (vi) co-clustering patterns of apoptotic and non-apoptotic cell surface receptors,
        (vii) production of pro-inflammatory cytokines,
        (viii) production of immuno-modulatory cytokines,
        (ix) markers of inflammation,
        (x) anti-apoptotic transcription factors,
        (xi) markers of ageing,
    (d) comparing the results obtained with a control.

17. The method according to claim 16, wherein the stress situation is a chemical stress, a biological stress or a physical stress.

18. The method according to claim 17, wherein the chemical stress is exerted by exposure to oxidants or carcinogens, or wherein the biological stress is exerted by exposure to bacteria, viruses, fungi, lipids derived from surrounding cells and/or microbes, or wherein the physical stress is exerted by exposure to UV-irradiation.

19. The method according to claim 16 to 18, wherein the pro-inflammatory cytokines are selected from the group consisting of IL-1, TNF-α, PGE-2, IL-6, IFN-γ or IL-8.

20. The method according to any of the claims 16 to 18, wherein the immuno-modulatory cytokines are selected from the group consisting of PAF, IL-10, IL-4 or TGF-ß.

21. The method according to any of the claims 16 to 18, wherein the lipids are selected from the group consisting of phospholipids, sphingolipids and glycosphingolipids.

22. The method according to any of the claims 16 to 18, wherein the markers of inflammation include Cox-2 and iNos.

23. The method according to any of the claims 16 to 18, wherein the anti-apoptotic transcription factors include AP-1 and NFkappaB.

24. The method according to any of the claims 16 to 18, wherein the markers of aging include elastases, collagenases, metalloproteinases, gelatinases, stromelysins, telo-merases.

25. Use of a substance according to any of the claims 1 to 5 or a composition according

to any of the claims 6 to 8 for decreasing multi-drug resistance of cancers.

26. The use according to claim 25, wherein the cancer is skin, gut or breast cancer.

27. Use of cells expressing and/or over-expressing CD_{1d} in an assay for screening for substances modifying and/or blocking CD_{1d} function.

28. Use of $CD_{1d}^{-/-}$ animals as a test model for determining the activity of substances influencing damages in epithelial tissues produced by a stress situation and/or hair loss.

29. Use of a substance according to any of the claims 1 to 5 in gene therapy.